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EXAMINER	
RAO, MANJUNATH N	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,199	BARANY ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 9-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 9-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 5, 9-27 are currently pending and are present for examination.

Applicants' amendments and arguments as well as the Declaration by Dr. Barany filed on 10-24-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the rejections under 35 U.S.C. 112, 1st paragraph (scope of enablement) and 2nd paragraph in view of persuasive arguments presented by the applicant. Examiner also acknowledges the amendment to the 1st line of the specification updating the relationship of the instant application to its parent application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 and claims 9-27 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase "and the distinguishing nucleotide is complementary to the oligonucleotide of the first oligonucleotide set having its 3' end at the first ligation junction". The entire phrase in the context of the claim is not clear to eh Examiner. It is not clear to the Examiner as to what applicants mean by "distinguishing nucleotide is complementary to the oligonucleotide" and how one skilled in the art knows where or which the "distinguishing nucleotide" is. The question is also how can a nucleotide be complementary to an entire oligonucleotide? A perusal of the specification to understand the meaning of the phrase in the context of the claim did not provide with any useful

definitions rendering the claim indefinite. Examiner requests clarification in the context of the above claim. Examiner suggests cancellation of the term which would eliminate the ambiguity without affecting the scope of the claim.

Claim 5 and claims 9-27 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase "wherein the at least two oligonucleotides hybridize on the first nucleotide sequence". It is not clear to eh Examiner whether the two oligonucleotides hybridize adjacent to each other on the first oligonucleotide or any where on the first oligonucleotide. If the oligonucleotides do not hybridize adjacent to each other then it is not clear as to how one skilled in the art can perform a ligase reaction.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the phrase "capturing a hook attached to at least one of the oligonucleotides..". The metes and bounds of the phrase specifically with reference to the term "hook" are not clear to the Examiner. It is not clear to the Examiner as to what applicants mean by the "hook". A perusal of the specification did not provide the Examiner with a clear definition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 27 is drawn to the method according to claim wherein the hybridization temperature is about 66 ° to 70 ° C. However, a perusal of the specification indicates that applicants have no support for the claimed hybridization temperature which now constitutes a "new matter". Therefore claim 27 is rejected for introducing "new matter" into the claims.

In response to the previous Office action, in which the rejection was made for claim 5 under 35 U.S.C. 112, 2nd paragraph as unclear for recitation of the phrases "denaturation treatment", "thermal hybridization treatment" and "detecting the presence", applicants have traversed. In their traversal applicants submit that one of ordinary skill in the art, having read the present application, would have understood fully how to carry out the claimed invention and pointed the Examiner to pg. 5, lines 24-30 for definition of hybridization treatment which is as follows:

> "at very high temperatures such as 94°C, virtually all double stranded DNA (independent of length) unwinds and melts. If one cools the temperature (to 45-65° C) in the presence of complementary oligonucleotides, they can hybridize to the

> correct sequences of the unwound melted DNA. DNA that has been melted and cooled in the presence of complementary oligonucleotides is now a substrate for the DNA ligase reactions."

It can be seen from applicant's own argument that the support for hybridization temperature is only from 45° C to 65° C which is entirely different then the temperature claimed in claim 27. Therefore, Examiner considers claim 27 as a "new matter" and suggests cancellation of the claim.

Claims 5, 9-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a first oligo DNA from a second oligoDNA by a cyclic reaction of annealing at about 50 degree C and denaturing at about 105 degree C and using a specific thermocyclable ligase enzyme having an amino acid sequence SEQ ID NO:2 or 8, wherein the detection is by gel electrophoresis of the reaction products, does not reasonably provide enablement for such a method of detecting any nucleotide sequence (for example RNA, PNA and such derived nucleotide sequences) comprising a cyclic reaction of annealing and denaturing tow nucleotide sequences at any temperature using any or all ligases including variants, mutants and recombinants and involving any or all methods of detecting the products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 5, 9-27 are so broad as to encompass detection of all types of nucleotide sequences, using any thermocyclable ligase (claim 5) and any reaction conditions (i.e., annealing and denaturing temperatures) and any method of detecting the products formed. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to a method of detecting any nucleotide sequence comprising the use of any or all ligases, including variants, mutants and recombinants of SEQ ID NO:2 and 8, any or all reaction conditions and detection procedures broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method comprising of detecting oligoDNA, using a specific thermocyclable ligase comprising the amino acid sequence SEQ ID NO:2 or 8 in a reaction condition comprising annealing/denaturing between 50 degrees and 105 degrees only and detection method comprising gel-electrophoresis only. It would require undue experimentation of the skilled artisan to practice the method for detecting any nucleotide sequence, using any ligase under any reaction condition and any method of detection of the product. The specification is limited to a method of detecting oligo DNA

using SEQ ID NO: 2 and 8 as a ligase and reaction conditions associated with the use of the above two polypeptides but provides no guidance with regard to the method of detecting any nucleotide sequence and comprising the use of any or all ligases, including variants, mutants and recombinants of SEQ ID NO:2 and 8, under any or all reaction conditions and detection procedures broadly encompassed by the claims. In view of the great breadth of the claim, amount of experimentation required to practice the method as claimed, the lack of guidance, working examples, and unpredictability of the art in predicting function and characteristics of a polypeptide from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques and general molecular biological techniques including DNA detection techniques are known, to practice a method as encompassed by instant claims, requires more guidance than that provided by the instant specification.

The specification does not support the broad scope of the claims which encompasses a method of detecting any nucleotide sequence comprising the use of any thermocyclable ligase because the specification does not establish: (A)a universal method of detecting any nucleotide sequence(i.e., DNA, RNA, PNA and other nucleotide derivative sequences) that can be performed using any or all ligases including the use of mutants, variants and recombinants under any reaction conditions; (B) does not provide any or all ligases including variants of SEQ ID

NO:2 or 8 that can be used in the claimed method; (C)the general tolerance of ligases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in a ligase with an expectation of obtaining the desired biological function (i.e., detecting any nucleotide sequences); and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of reaction conditions is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to practice the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for detecting any nucleotide sequence comprising the use of any or all ligases under any or all reaction conditions. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the claimed method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants have traversed the above rejection. Applicants submit that the making of the claimed invention is taught in such complete and sufficient detail in the present application that one of ordinary skill in the art would have been fully able to make and use the present invention. Applicants argue that it would have been well within the capabilities of one skilled in the art to determine, without undue experimentation, whether a given ligase is thermocyclable, i.e., whether it does or does not become irreversibly denatured and lose its catalytic activity when subjected to temperatures ranging from about 50° C to 105° C and that the application discloses in Example V that it is known in the art

that thermophilic proteins may be substantially modified and still retain sufficient activity for use in the present invention (pg. 34, line 29 to pg. 35, line 12) and therefore, one skilled in the art would expect that following the guidance provided in the specification, thermocyclable ligases other than those having SEQ ID NO: 2 and NO: 8 could be prepared and used in the claimed invention. Examiner respectfully disagrees. This is because, while the specification may teach general guidelines for making variants, it is silent as to where or which specific amino acids in the ligase sequence can be modified such that the ligase retains all the characteristics of the parent ligase so that it can be used in the claimed method. Contrary to applicant's argument, without such guidance one of ordinary skill in the art would be reduced to the necessity of producing and testing all of the possible variants. The art clearly *does not* typically engage in the screening of such large number of to isolate those relatively few variants that would have the desired activity. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

Next, applicants argue, in particular, a skilled scientist would have known the specific characteristics to look for in such a ligase, because the specification teaches that a ligase in accordance with the present invention is useful for amplifying DNA and discriminating single base substitutions in a DNA (see page 40, lines 7-10 of the present application) and that "the single most important property" of the ligase of the present invention is that it "retains activity during repeated thermal denaturation/renaturation cycles thus allowing for the amplification of

DNA without necessitating repeated addition of ligase" (see page 40, lines 10-13 of the present application). While that may be so, instant claims are limited to detecting or amplifying only DNA. Current claims are directed to a method of detection of any nucleotide sequence which encompasses DNA, RNA, PNA or any such nucleotide derived sequences. Applicants have not clearly shown in any of the examples in the application that the ligase they provide is capable of performing detection and amplification of any or all nucleotide sequences.

Applicants continue their argument that the ligase of the present invention will ligate *oligonucleotides* of a length which is sufficient to assure their uniqueness in complex genomes at or near the T_m temperatures of 65° C, and will also accurately discriminate between exactly complementary and single based mismatched oligonucleotide sequences." (see pg. 40, lines 10-17.) and therefore it is apparent that the present application contains extensive ligase disclosure largely to support claims (not pending) which are directed to a ligase *per se*. and with regard to the claimed method of detecting, it is clear that applicants did not try to patent a new ligase, but, rather, a new and unobvious method for detection useful with a variety of thermocyclable ligases and that it is entirely inappropriate to attempt to limit patent coverage for that method to specific ligases when others would clearly work. Examiner respectfully disagrees with such an argument. As argued above by the Examiner the claims are not commensurate with the scope. Claims are not only claiming a broad method of detecting and amplifying any nucleotide sequence, the claimed method encompasses ligases that cannot be used to fully appreciate the scope of the claimed method. Therefore the above rejection is maintained.

Claims 5 and 9-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5 and 9-27 are directed to a method comprising the use of ligase polypeptides including variants, mutants and recombinants of SEQ ID NO:2 or 8. Claims 5 and 9-27 are rejected under this section of 35 USC 112 because the claims are directed to the method of use of a genus of polypeptides including those derived from SEQ ID NO:2 or 8 (including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 or 8 and fragments of SEQ ID NO:2 or 8) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 or 8 have been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2 or 8, including fragments and variants within the scope of the claimed genus. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a two species of the genus for use in the claimed method which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one

skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to he previous Office action, applicants have traversed the above rejection arguing that one of ordinary skill in the art having read the present application, would have understood that the inventors were in full possession of the invention as claimed and that the rejection is another inappropriate attempt to limit the claims to the ligases actually utilized when it is readily apparent that other ligases could also be used. Applicants argue that what applicants made and claim is a new and unobvious method and not a ligase. Examiner respectfully disagrees. While it is agreed that applicants are claiming a method and not a ligase, the method is drawn to the to he use of a genus of ligases which have not been described. While applicants argue that any thermocyclable ligase can be used, the method as claimed does not appear to be so. For example, the method claims the sequence of nucleotides complementary to the first nucleotide sequence is amplified by 100 fold in 5 to 20 cycles and the first nucleotide sequence can be distinguished in a sample even present down to amount of 1 femtomole and the low percent mismatches that occurs in the reaction. These are all highly specific results obtained in the method which can be obtained using specific thermocyclable ligase. Even the Declaration by Dr. Barany is devoted to describing these characteristics of the reaction as that which can be obtained only by the use of *Tth* ligase, as unexpected results which cannot be seen by using any ligase.

Applicants next argue that the present application teaches, in detail, how the claimed ligase is made and used and that one of ordinary skill in the art, having read the present application, would understand that at the time the application was filed, applicants were in possession of the claimed method and therefore, the rejection of claims under 35 U.S.C. §112 for failure to meet the written description requirement should be withdrawn. Examiner respectfully disagrees. Contrary to applicant's argument, the claims in the application are drawn to a method and not to the ligase and a method of its use. However, the claimed method encompasses the use of a genus of ligases whose structures have not been disclosed in the specification. As discussed in the written description guidelines, the written description requirement for the use of a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing

only one species within the genus. In the instant case the claimed method discloses the use of a genus which includes species which are widely variant in structure. The genus is structurally diverse as it encompasses a variety of ligases. As such, neither the description of the structure and function of SEQ ID NOS:2 and 8 nor the disclosure solely of functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 9-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren et al. (Science, 1988, Vol. 241 (4869):1077-1080 cited in the IDS), Wu et al. (Gene Vol. 76 :245-254, 1989 cited in the IDS) and Takahashi et al. (J. Biol. Chem., 1984, Vol. 259(16):10041-10047 cited in the IDS). Claims 5, 9-27 of the instant application are drawn to a method of detecting a nucleotide sequence using a thermocyclable ligase enzyme which does not become irreversibly denatured and lose its catalytic activity when subjected to temperatures ranging from 50 degree C to 105 degree C and which ligates two single stranded DNA hybridized to another single strand DNA. The method involves subjecting the mixture of the DNAs to denaturation, hybridization, and ligation by said ligase for several cycles followed by detection of the ligated oligonucleotide DNAs. Claims are also drawn to several limitations

such as the method amplifies the first nucleotide sequence by about 50 to 500 fold more than if a single base mismatch were present at the ligation junction, by at least about 100 fold more than if the first nucleotide sequence were not present in the sample, wherein the number of cycles is about 5 to 20, wherein the first nucleotide sequence can be distinguished in the sample when present down to 1 femtomole, A:A mismatch percentage of 0.4 to <0.1%, T:T mismatch percentage of 0.7 to 1.0%, G:T mismatch percentage of 1.0 to 1.5%, C:T mismatch percentage of 0.4 to <0.1%, G:A mismatch percentage of 0.4 to <0.1%, C:A mismatch of 0.4 to <0.1% etc.

Landegren et al. or Wu et al. indeed teach an identical method. Landegren et al. teach an assay to detect the presence of a given DNA based on the ability of two oligonucleotides to anneal immediately adjacent to each other on a complementary target DNA molecule which are then ligated by a DNA ligase provided that the nucleotides at the junction are correctly base-paired. The reference also states that such a method can be used for rapid and standardized identification of genomic DNA (also see Figure 1 on page 1078) by denaturing, annealing (hybridizing) and ligating. The method disclosed by Landegren is identical to the method except for the use of a thermocyclable ligase in the instant claims.

Wu et al. also disclose an identical method wherein the method uses a T4 DNA ligase. In fact, applicants themselves admit that Wu et al. disclose such a method and is capable of amplifying the DNA starting with 500,000 copies in 95 hours, using 75 cycles of denaturing, annealing and followed by detecting (see page 4 of the specification).

The above two references teach an identical method of detecting a given DNA in a sample. However, both the references do not teach the use of thermocyclable ligase that can withstand temperatures ranging from 50 degree C to 105 degree C.

Takahashi et al. teach a thermocyclable ligase enzyme and its properties. Takahashi et al. teach the purification and properties of a DNA ligase isolated from *T.thermophilus* HB8 which is also known as *T.aquaticus* HB8 in the art and which is identical to the enzyme of the instant application and which exhibits identical thermostable properties.

With all the above three references in hand it would have been obvious to those skilled in the art to use the thermostable enzyme taught by Takashi et al. in the assays and detection reaction taught by Landegren et al. or Wu et al. One of ordinary skill in the art would have been motivated to do so since using the enzyme of Takahashi et al. would eliminate the requirement of replenishing the ligase enzyme after each cycle of denaturation and annealing. One of ordinary skill in the art would have a reasonable expectation of success since Takashi et al. provide the thermocyclable ligase and Landegren et al. or Wu et al. provide the basic ligase detection method.

Therefore the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In response to the previous Office action, applicants have traversed the above rejection arguing that neither Landegren nor Wu et al. teach or suggest a method of detecting nucleotide sequence using a thermocyclable ligase and that while Takahashi et al. teach a thermocyclable ligase, that ligase has the ability to ligate thymidylate oligomers in the presence of poly(dA) as a template with nick closing activity and that proper *prima facie* showing of obviousness requires the USPTO to satisfy three requirements, first the prior art relied upon, coupled with the knowledge generally available to one of ordinary skill in the art must contain some suggestion to motivate, second, the Office must show that at the time the invention was made the proposed modification had a reasonable expectation of success and finally, the combination of references must teach or suggest each and every limitation of the claimed invention. Applicants argue that there is no suggestion in Takahashi et al. that its ligase is useful in carrying out the procedure disclosed by Landegren and Wu et al. and more particularly, there is no indication in Takahashi et al. that the ligase disclosed would not interfere with, let alone be useful in, steps of hybridizing oligomers to a DNA template or denaturing strands of hybridized DNA. Examiner respectfully disagrees with such an argument. Contrary to applicant's argument Examiner takes the position that he has satisfied all the three requirements for a *prima facie* obvious case in his rejection. First at the time of invention, the PCR technique which involved the use of thermocyclable polymerase and the method of amplifying DNA by cycling between annealing and hybridization was well known. The advantages of such cycling reaction in terms of speed, recovery of the DNA and even detection of DNA in a given sample was well known and appreciated by those skilled in the art. In fact, the PCR reaction was also used to detect and amplify small amount of sample DNA. While this technique of detecting/amplifying DNA is not essentially the same as

that claimed herein, the use of denaturation/hybridization cycling in the presence of a thermostable enzyme for DNA substrate was well known in the art. With such knowledge already well known in the prior art, it would have been obvious to those skilled in the art to repeat the procedure of Wu et al. or that of Landegren et al. by using the enzyme provided by Takahashi et al. even in spite of the fact that Takahashi et al. make no suggestion for use of their enzyme in the procedure of Wu et al. or Landegren et al. The advantages of using the thermocyclable enzyme would have been self-evident to those skilled in the art. Therefore applicant's argument that there is no case of obviousness because there is no suggestion in the reference of Takahashi et al. is highly misplaced. Next, applicant's argument that the enzyme of Takahashi et al. would some how interfere in the hybridization step is also highly misplaced. This is because Examiner was unable to find any such information either in the reference of Takahashi et al. or in the scientific literature in general that certain ligases or even polymerases in thermocycle reaction interfere with the hybridization of the templates. At best, applicant's argument is a conjecture that the enzyme interferes in the hybridization step and is devoid of any scientific evidence.

Next, applicants argue that at best, the combination of references constitutes nothing more than impermissible "obvious to try" position. Applicants argue that even if one skilled in the art would have thought to combine the thermostable enzyme of Takahashi et al. in the procedure of Wu et al. or Landegren et al., there would have been absolutely no guidance on how to identify a ligase useful in the methods taught by Wu et al. or Landegren et al. and the reader would be left to choose amongst available enzymes and try to find one which is useful and there is no guidance to proceed. Again Examiner respectfully disagrees with such a tangential

argument. Furthermore, the above argument by applicant is fully contradictory to their own argument they have made against the enablement rejection, in which they have argued that those skilled in the art would know to use any available thermostable ligase for the claimed method and that the single most important property of the ligase for the claimed method would be for the ligase enzyme to retain the activity during repeated thermal denaturation/renaturation cycles thus allowing amplification of DNA without necessitating repeated addition of ligase. It would have been obvious to those skilled in the art to recognize such a property in the enzyme of Takahashi et al. and therefore substitute it in the method of Wu et al. or that of Landegren et al. In response to applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, as argued above, the importance of thermocyclable enzymes with respect to DNA detection and amplification was already well known in the art (Polymerase chain reaction). Therefore, applicant's allegation that the Examiner is reporting to improper hindsight reasoning does not hold.

Finally, applicants take refuge by declaring unexpected results in their method and their ligase enzyme. Referring to the Declaration of Dr. Barany applicants argue that the *Thermus thermophilus* ligase discriminates mismatches at the 3' side of the nick much more efficiently than those placed on the 5' side of the nick, contrary to the expected fidelity to be better for

mismatches at the 5' side of the nick. This, applicants claim was unexpected of their enzyme and such evidence of unexpected results will rebut *prima facie* case of obviousness. Applicants argue that even though there is no *prima facie* case of obviousness, it is rebutted by the above experimental data. Examiner respectfully disagrees with such an argument. First of all Examiner takes the position that there is a *prima facie* case of obviousness. Furthermore, Examiner does not give any credence to the unexpected results. This is because, applicants method is not limited to the use of a specific ligase enzyme or in particular the ligase enzyme of *Thermus thermophilus*. The claimed method is open to use any thermocyclable ligase and the specification does not teach a method comprising specific steps that when followed would result in such fidelity when the method is performed by using any thermocyclable ligase. Therefore, applicant's argument that they have unexpected result is totally misplaced. In view of all the above, contrary to applicant's argument the combination of teachings of the above references renders the above claims *prima facie* obvious to one of ordinary skill in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

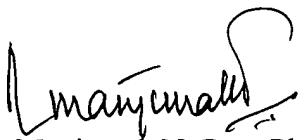
Claims 5, 9-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17, 22, 24, 26, and 28 of U.S. Patent No.5,830,711. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 5, 9-27 of the instant application and claims 1-17, 22, 24, 26, and 28 of the reference patent are both directed to method of detection/distinguishing polynucleotide sequences in a thermocycle reaction using a thermocyclable ligase. Among all the different steps and limitations claimed in the instant application and in the reference patent a good number of steps and limitations are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the recited steps and limitations includes several embodiments that would anticipate the steps and limitations claimed in claims 5, 9-27 herein. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-17, 22, 24, 26, and 28 of the reference patent when there is specifically recited embodiment that would anticipate mainly claim 5 of the instant application. Alternatively, claims 5, 9-27 cannot be considered patentably distinct over claims 1-17, 22, 24, 26, and 28 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-17, 22, 24, 26, and 28 of that patent and falls within the scope of claims 5, 9-27 herein because it would have been obvious to

one having ordinary skill in the art to modify claim 1 of the reference by selecting a specifically disclosed embodiment that supports that claim. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claim 1 of the reference patent.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

January 7, 2006